

Clinical Trial Design

*Sponsored by
Center for Cancer Research
National Cancer Institute*



Overview

Clinical research is research conducted on human beings (or on material of human origin such as tissues, specimens, and cognitive phenomena) with the goal of generating useful knowledge about human health and illness. A clinical trial is one type of clinical research that seeks to answer a scientific or medical question about the safety or potential benefit of an intervention such as a medication, device, teaching concept, training method, or behavioral change.

This module will provide an overview of clinical trial design. At the conclusion of this module, the learner will be able to:

- Describe five types of clinical trials.
- Discuss the objectives, endpoints and standard design for Phase I, II, and III clinical trials.

Types of Clinical Trials

- Natural History
- Prevention
- Screening and Early Detection
- Diagnostic
- Quality-of-life and supportive care
- Intervention/Treatment

Natural History Trials

A prospective study to determine the natural course of cancer when:

- Left untreated
- Treated with standard therapy

Prevention Trials: *Chemoprevention*

- Evaluate the effectiveness of ways to reduce the risk of cancer
- Enroll healthy people at high risk for developing cancer
- 2 types of trials:
 - Action studies – “do something”
 - Agent studies – “take something”



Screening and Early-Detection Trials



- Assess new means of detecting cancer earlier in asymptomatic people
- Tools:
 - Tissue sampling/procurement
 - Laboratory tests, including genetic testing
 - Imaging tests
 - Physical exams
 - History, including family hx (pedigree)

Diagnostic Trials

- Develop better tests or procedures to identify a suspected cancer earlier or more accurately
- Tools:
 - Imaging tests
 - Laboratory correlative studies/tumor marker

Supportive Care/QOL Trials

- Evaluate improvements in comfort of and quality of life (QOL) for people who have cancer
- Seek better therapies or psychosocial interventions for subjects
- Focus on subjects AND families or caregivers

Imaging Trials

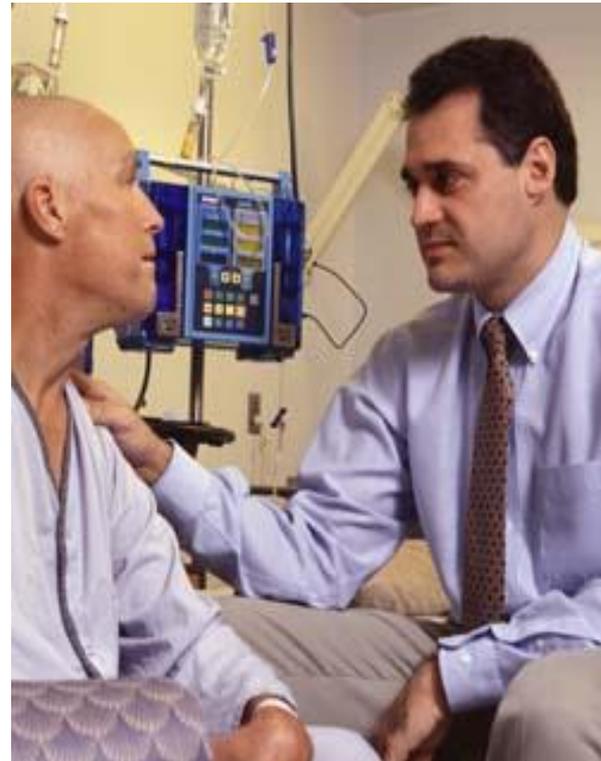
Imaging clinical trials differ from drug treatment trials in that the scientific question being asked is aimed at understanding if or how a specific imaging test can best be used to screen, diagnose, direct the treatment of, or monitor the response to a therapy for a disease.

Types of Imaging Trials

- **Screening for cancer**
 - determine if a person has any suspicious areas or abnormalities that might be cancerous.
- **Diagnosis/staging**
 - used to find out where a cancer is located in the body, if it has spread, and how much is present
- **Guiding cancer treatments**
 - used to make cancer treatments less invasive by narrowly focusing treatments on the tumors
- **Determining if a treatment is working**
 - used to see if a tumor is shrinking or if the tumor has changed and is using less of the body's resources than before treatment
- **Monitoring for cancer recurrence**
 - used to see if a previously treated cancer has returned or if the cancer is spreading to other locations

Treatment Clinical Trials

- Test new treatments, new combination of drugs, or new approaches to surgery or radiation therapy
- 4 Phases



Phases of Clinical Trials

Phase I Trial

To determine the appropriate dose for further evaluation

Phase II Trial

To determine whether an agent has activity against a specific cancer type

Phase III Trial

To determine whether a treatment is effective

Phase IV Trial

Post FDA approval, various goals

Phase I: Primary Goal(s)

Evaluate Toxicity:

- Define dose limiting toxicity (DLT)
- Define maximum tolerated dose (MTD)
- Begin development of side-effect profile

Evaluate Pharmacokinetics PKs): ADME

How the drug(s) is:

- Absorbed
- Distributed
- Metabolized
- Excreted

May provide early evidence of response, but
NOT primary aim

Phase I: Additional Goal(s)

- Also used to:
 - Evaluate new treatment schedule
 - Evaluate new drug combination strategy
 - Evaluate new multi-modality regimen

Phase I: Patient Population

- 15 – 30 (< 100) subjects
- Usually many cancer types (e.g. solid tumors)
- Refractory to standard therapy
- No remaining standard therapy
- Adequate organ function
- Adequate performance status

Phase I: Standard Design

- Open label, non-randomized, dose escalation
- Low starting dose
 - $1/10^{\text{th}}$ the lethal dose (LD10) in the most sensitive species tested = dose at which 10% of the animals die
 - Unlikely to cause serious toxicity
 - Pediatric dose starts at 80% of adult MTD
- 3-6 patients per cohort
- Increase dose gradually
 - Most common scheme is a Modified Fibonacci

Classic Modified Fibonacci Dose Escalation Scheme

% Increase Above Preceding Dose:

Level 1: Starting dose

Level 2: 100% increase from Level 1

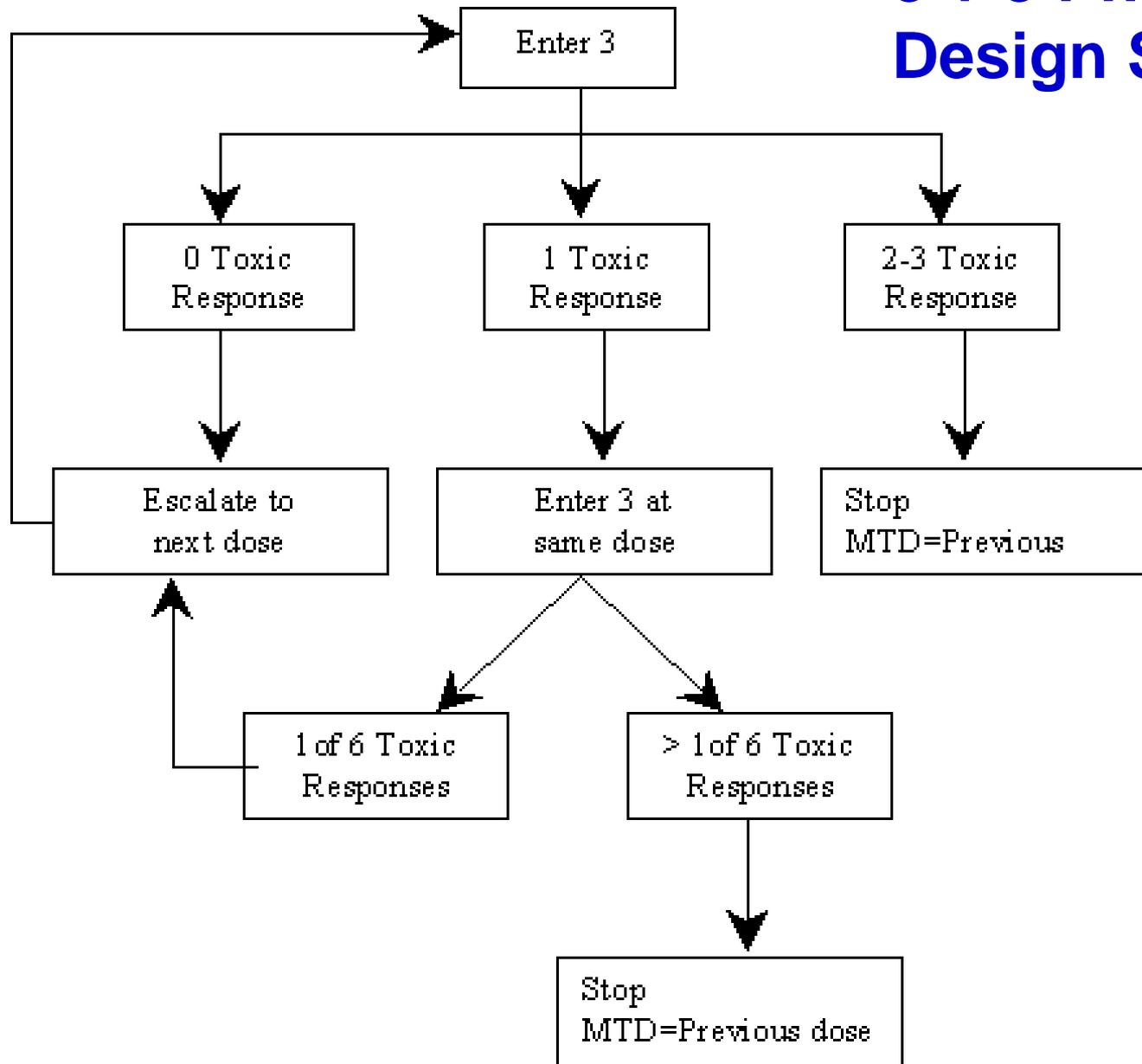
Level 3: 67% increase from Level 2

Level 4: 50% increase from Level 3

Level 5: 40% increase from Level 4

Levels 6+: 33% increase from Level 5+

3 + 3 Phase 1 Study Design Schematic



Alternate Designs

In addition to the 3 + 3 standard design, we are beginning to see alternate designs:

- “Accelerated” design:
 - E.g.: 1 subject enrolled per dose level until one grade 2 adverse event that is related to the investigational agent(s) is seen. Then the design returns to the 3 + 3 design as per previous schematic.
- “Inpatient dose escalation”:
 - E.g.: once a dose level has been proven “safe” (not the MTD) then subjects at lower levels are able to escalate to the “safe” level
 - E.g.: once a subject is able to tolerate a dose level (no DLT) they are allowed to escalate to the next level using themselves as the own control

Phase I: Endpoints

- Dose Limiting Toxicity (DLT)
 - General DLT Criteria:
 - \geq Grade 3 non-heme toxicity
 - Grade 4 neutropenia lasting longer than 5 days
 - Grade 4 thrombocytopenia
 - Typically the DLT is defined for the first course/cycle
- Maximum Tolerated Dose (MTD)
 - Highest dose level at which $\leq 1/6$ patients develop a DLT

Phase I: Limitations

- Questionable risks without benefits
- Initial patients may be treated at low (sub-therapeutic) doses
- Slow to complete trial (need to find fairly healthy advanced cancer patients)
- Toxicity may be influenced by extensive prior therapy
- Inter-patient variability
- MTD definition is imprecise
- Minimal data about cumulative toxicity since only the first cycle/course is taken into consideration for a DLT

Phase II: Primary Goals

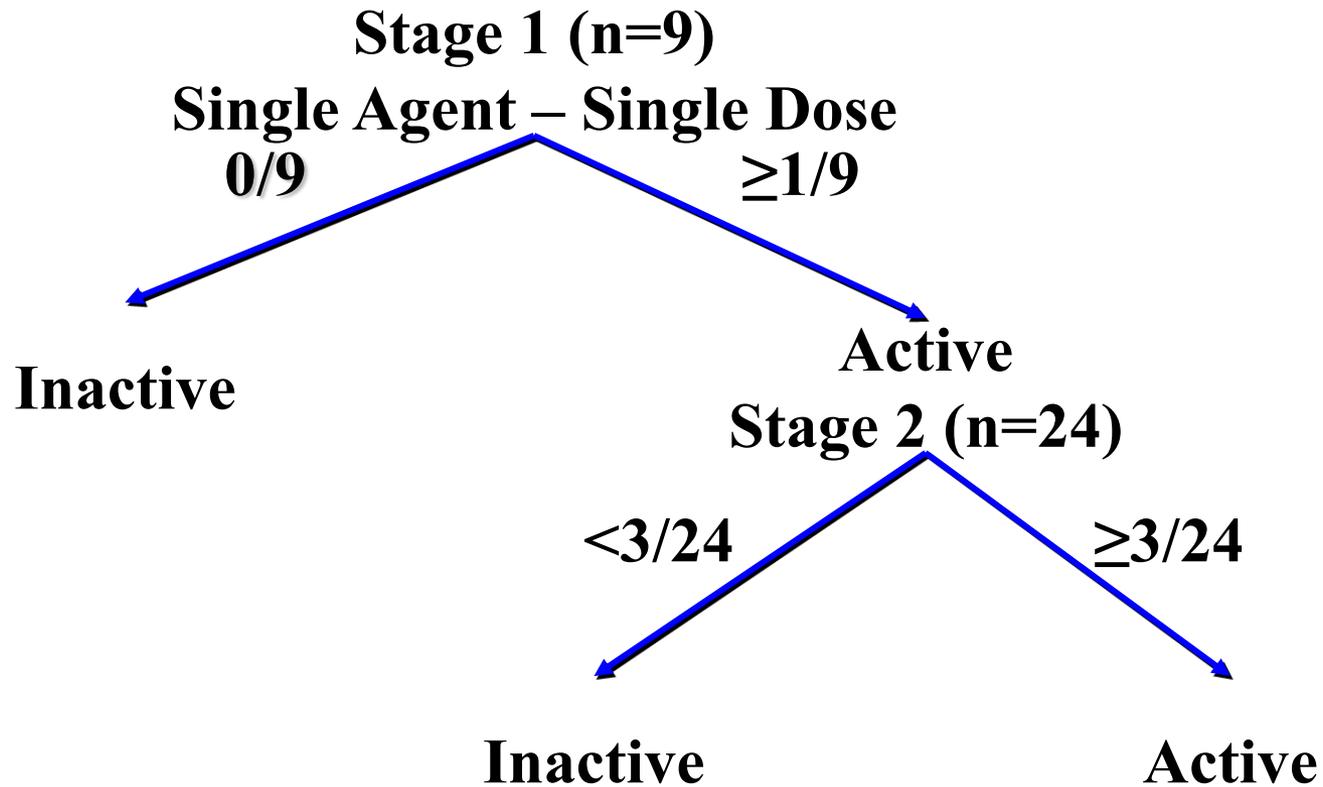
Evaluate activity

Further safety (adverse events) evaluation
at the MTD

Phase II: Patient Population

- ~100 subjects (100-300)
- More homogenous population that is deemed likely to respond based on:
 - phase I data
 - pre-clinical models, and/or
 - mechanisms of action
- Subject needs to have measurable disease
- May limit number of prior treatments

Phase II: Standard Design



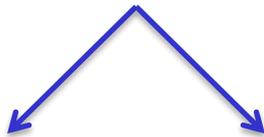
Two-stage design with early stopping rule for efficacy or futility

Phase II: Alternate Design...

Low dose vs. higher dose

Randomization (n=50)

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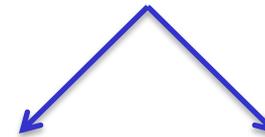
New Agent/
Intervention
Low Dose

New Agent/
Intervention
Higher Dose

Placebo (Inactive) vs agent

Randomization (n=50)

25



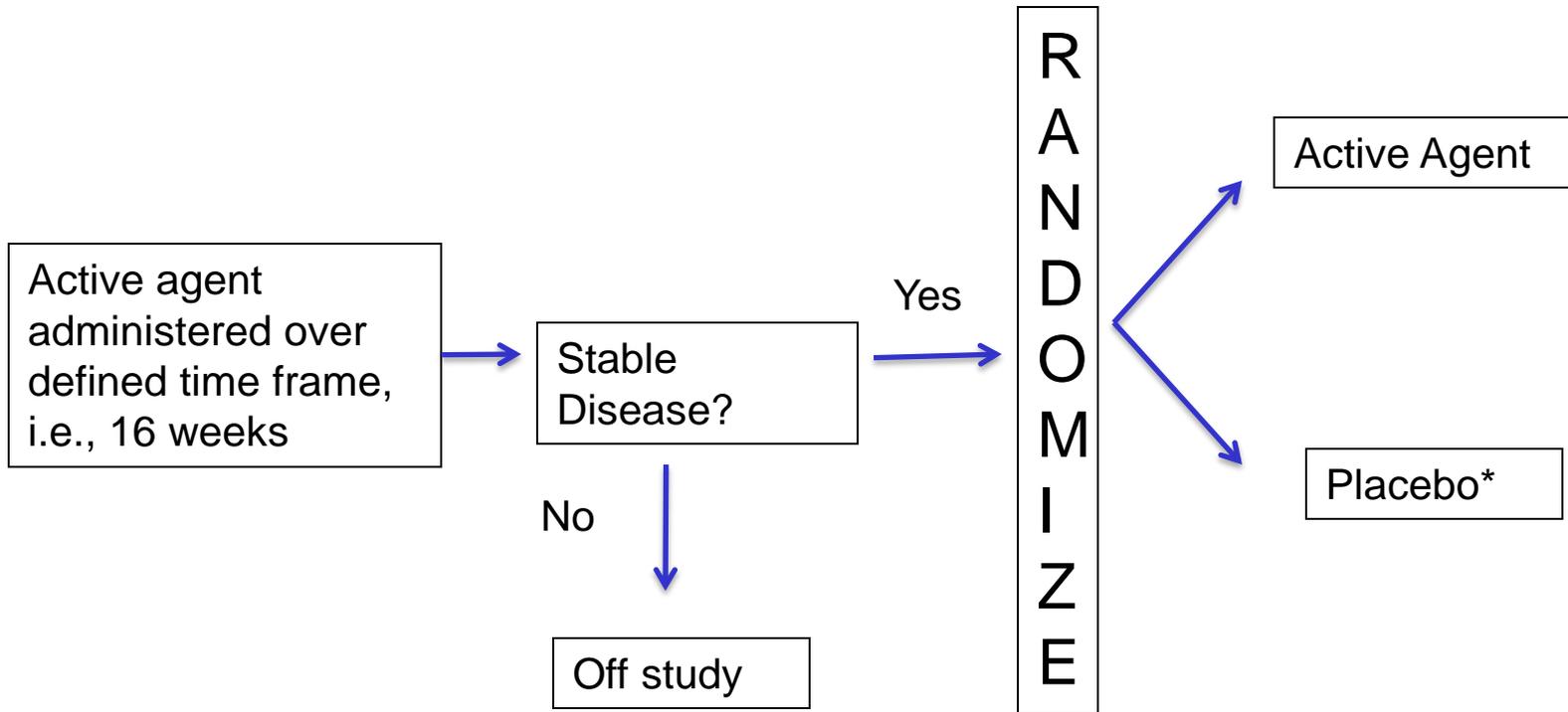
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New agent
alone or
+ placebo

New agent +
standard of
care

...Phase II: Alternate Design

Randomized Discontinuation Design



* Patients with progressive disease on placebo can switch back to active agent.

Phase II: Endpoints

- Response (see response assessment module for more details)
 - Complete Response (CR)
 - Partial Response (PR)
 - Stable Disease (SD)
 - Progressive Disease (PD)
- Additional safety data

Phase II: Limitations

- Lack of activity may not be valid
- Measurable disease required
- No internal control group

Phase III: Primary Goals

Efficacy compared to standard therapy

- Activity demonstrated in Phase II study

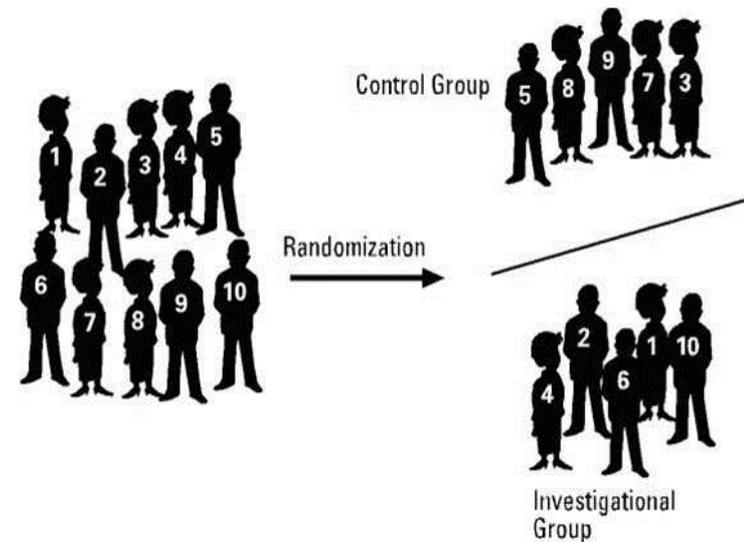
Further evaluation of safety

Phase III: Patient Population

- Hundreds to thousands of subjects
- Single cancer type
- May be front-line therapy
- Well-defined eligibility criteria
- Internal control group (e.g., standard treatment, placebo)
- Multi-institutional participation necessary to reach targeted accrual goals

Phase III: Standard Design

- Randomized assignment of patients to treatment arms
- Equal distribution of known important prognostic factors to each arm (stratification)



Phase III: Other Considerations

- Sample size chosen to detect difference
- Intention-to-treat analysis may be used
 - strategy for the analysis of randomized controlled trials that compares patients in the groups to which they were originally randomly assigned whether they complied with the treatment they were given
- Data Safety Monitoring Committee/Board (DSMC/DSMB) for interim analysis

Randomized Study Designs

Two Commonly Used Randomized Designs:

- Parallel Group Design
 - Subject randomized to 1 of 2 or more arms with each arm being a different treatment
- Crossover Design
 - Subject randomized to a sequence of 2 or more treatments
 - Subject acts as own control
 - May “crossover” to other treatment for progressive disease
 - May “crossover” to other treatment after treatment course completed

Phase III: Endpoints

- Efficacy
 - Overall survival
 - Disease-free survival
 - Progression-free survival
 - Symptom control
 - Quality of life

Phase III: Limitations

- Difficult, complex, expensive to conduct
- Large number of patients required
- Incorporation of results into front-line therapy in community is often slow and incomplete

FDA Cancer Approval Endpoints

- Overall survival
- Endpoints based on tumor assessments
- Symptom endpoints (PROs)

The next few slides will define the endpoints.

Overall Survival

- Time from randomization until death
- Intent-to-treat population

Endpoints: Tumor Assessments...

- **Disease-free survival**
 - Randomization until recurrence of tumor or death from any cause
 - Adjuvant setting after definitive surgery or radiotherapy
 - Large % of patients achieve CR after chemo
- **Objective response rate (ORR)**
 - Proportion of patients with reduction of tumor size of a predefined amount and for a minimum time period
 - Measure from time of initial response until progression
 - Sum of PRs + CRs
 - Use standardized criteria when possible

...Endpoints: Tumor Assessments

- **Progression free survival (PFS)**
 - Randomization until objective tumor progression or death
 - Preferred regulatory endpoint
 - Assumes deaths are r/t progression
- **Time to Progression (TTP)**
 - Randomization until objective tumor progression, excluding deaths
- **Time-to-treatment failure (TTF)**
 - Randomization to discontinuation of treatment for any reason (PD, toxicity, death, etc.)
 - Not recommended for regulatory drug approval

Endpoints: Symptom Assessment

- Time to progression of cancer symptoms
- FDA Guidance: *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*
- Tools/surveys
- Issues:
 - Missing data
 - Infrequent assessments

Phase IV Trial

Follow-up investigation to further evaluate long-term safety and effectiveness of a recently approved drug:

- Further assess risk/benefit ratio
- Further evaluation of efficacy
- Further evaluation of toxicity
- Further evaluation in other populations (e.g., elderly)
- Facilitate integrate new treatment into primary therapy
- Costly to conduct so often not done

References

- Adjei, A.A., Christian, M., Ivy, P. (2009). Novel Designs and End Points for Phase II Clinical Trials. *Clinical Cancer Research*, 15(6), 1866-1872.
- Kummar, S., Gutierrez, M., Doroshow, J., Murgu, A.J. (2006). Drug development in oncology: classical cytotoxics and molecularly targeted agents. *British Journal of Clinical Pharmacology*, 62(1), 15-26.

Websites

- FDA IND application
- FDA Guidance: *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*
- FDA Guidance: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Evaluation

Please complete the [evaluation form](#) and fax to Elizabeth Ness at 301-496-9020.



For questions, please
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